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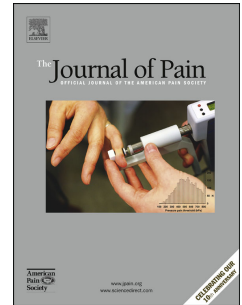
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# Accepted Manuscript

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# Is pain perception altered in people with depression? A systematic review and meta-analysis of experimental pain research

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## Disclosures

BS, TT and KG have no conflicts of interest.

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**Abstract**

While clinical studies suggest depressed patients may be more vulnerable to pain, experimental research is equivocal. This meta-analysis aimed to clarify whether depression is associated with altered pain perception in response to noxious stimulation and to identify factors that might influence this association. A search of major electronic databases was conducted to identify experimental studies investigating pain response in depressed participants vs. healthy controls using established pain outcome measures. Random effects meta-analysis of standardized mean differences was conducted on data from 32 studies ( $N=1,317$ ). For high-intensity noxious stimulation, overall pain tolerance was similar across depressed and control groups (Hedge's  $g=0.09$ ,  $p=0.71$ , studies=10). For low-intensity stimulation, a small, but statistically significant higher mean sensory threshold ( $g=0.35$ ,  $p=0.01$ , studies=9) and pain threshold ( $g=0.32$ ,  $p=0.02$ , studies=25) was observed in depressed participants, suggesting diminished pain. However, considerable heterogeneity in the direction and magnitude of effects was observed, indicating a likely condition-specific impact of depression on pain. Subgroup analysis found that pain threshold/tolerance was increased in depression for exteroceptive (cutaneous) stimulation but decreased for interoceptive (ischemic) stimulation, but that substantial heterogeneity remained. Overall, results provide some support for altered pain processing in depression, but suggest this link is dependent upon modality and additional, unidentified factors.

**Perspective**

This meta-analysis of experimental studies suggests potential effects of depression on pain perception are variable and likely to depend upon multiple factors. The contrasting pattern for ischemic vs. other noxious stimuli suggests that stimulus modality is a key factor, which could help explain discrepancies across clinical and experimental findings.

*Key words:* Depression; depressive disorder; pain; meta-analysis; systematic review.

## Introduction

Depression and pain are frequently observed as comorbid conditions in clinical settings. They represent two of the leading predictors of years lived with disability across the world<sup>73</sup>, and appear to interact to prove costlier and more disabling than the sum of their individual effects<sup>2</sup>. Patients with depression often present with medically unexplained somatic complaints, such as abdominal pain, back pain and headache<sup>35</sup>, with mean pain prevalence estimated as 65%<sup>2</sup> compared to around 29% for non-depressed populations<sup>15</sup>. Moreover, the presence of depression may predict future musculoskeletal pain<sup>40</sup> and is a key risk factor for chronic low back pain<sup>53</sup> suggesting a causal influence. The biochemical theory of depression suggests that a neurochemical imbalance of monoamines (e.g. serotonin) underlies depression and, given that these neurotransmitters are likely to play a key role in modulatory pain pathways, this may lead to altered pain perception<sup>2,27</sup>. Neural mechanisms common to depression and pain have also been implicated, with areas of the brain linked to mood (e.g. amygdala, insular) also sending numerous projections to key structures involved in pain modulation (e.g. periaqueductal gray)<sup>2,22</sup>.

If pain perception abnormalities are a manifestation of depression, this may have important treatment and diagnostic implications. For example, Fishbain et al.<sup>24</sup> found that the impact of antidepressant medication on depression response/remission may be impaired when pain is present. Pain may also influence diagnostic accuracy, with failure to accurately diagnose major depression by physicians estimated to exceed 50%<sup>31,46</sup>, with presence of painful symptoms being central to misdiagnosis<sup>13,32</sup>. One large review found that 69% of individuals experiencing depression tended to disclose *only* somatic symptoms<sup>59</sup>, explaining why depression is frequently misdiagnosed as a somatic illness<sup>71</sup>. The consequences of failing to recognize depression can be severe, as untreated depression often becomes worse, leading to poorer outcomes<sup>55</sup>.

Pain perception abnormalities in depression have also been examined using experimental paradigms to provide a level of control difficult to achieve in clinical settings, and to facilitate the assessment of pain across multiple dimensions, including subjective, behavioral and psychophysiological responses. Surprisingly, a preliminary meta-analysis of six experimental studies<sup>16</sup> found *decreased* pain in depressed groups relative to healthy controls. Whilst informative, a considerable number of studies have been conducted since the publication of the original review 13 years ago. Furthermore, limited data availability restricted the review to an examination of pain threshold only, which assesses minimal intensity pain<sup>75</sup>, and which in isolation is of limited clinical relevance. Since this review, there has been mounting interest in depression and pain perception with many experimental studies conducted over the past decade, producing equivocal findings. One possible explanation for this equivocality is that the link between depression and pain perception may be dependent upon the type of noxious stimulus used, with one theory<sup>37</sup> suggesting that different sources of pain (e.g. exteroceptive vs. interoceptive) are subserved by distinct pain inhibitory systems and these can be affected differentially by depression. While preliminary evidence appears to support this theory, the influence of stimulus modality as a possible moderator has yet to be subject to systematic review. To better understand the link between depression and pain, there is a pressing need to provide an updated review and synthesis of the recent experimental pain literature, examining potential moderators and more clinically relevant measures, such as pain tolerance<sup>75</sup>, pain affect and pain intensity ratings.

Therefore, we conducted a comprehensive systematic review and meta-analysis comparing depressed and healthy control groups in their response to experimentally-induced pain. Specific aims were to examine: (1) whether depressed vs. healthy controls differed in sensitivity to experimentally-administered noxious stimuli, (2) whether differences would

be confined to specific pain outcomes, and (3) which variables moderated the observed effects.

## **Method**

This systematic review was conducted in accordance with the MOOSE guidelines<sup>64</sup> and the PRISMA statement<sup>47</sup>.

### *Eligibility criteria*

Studies were included that utilized: (1) a group with current depression, as defined by a primary diagnosis of a depressive disorder based on a clinical instrument (e.g. DSM, ICD) or a standardized questionnaire (e.g. the Beck Depression Inventory); (2) a comparative control group of healthy, non-depressed individuals; (3) an experimental sensory stimulus; and (4) at least one of the following outcome measures: pain threshold, pain tolerance, pain ratings or sensory threshold.

Studies were excluded if: (1) depression was a secondary diagnosis, (2) depressed groups suffered from a chronic pain condition, (3) classification as depressed was based on experimental mood induction, or (4) pain perception was assessed during an experimental manipulation of mood or attention.

### *Information sources and search details*

Two independent reviewers (KG, TT) searched EMBASE, MEDLINE, PsycINFO and the Web of Science from database inception until 7<sup>th</sup> April, 2015. Our search used a widely inclusive strategy, identifying articles that contained appropriate combinations of broad and specific keywords relating to eligibility criteria; precise search term combinations are reported in Table S1 along with number of hits returned for the Medline database as an exemplar. Due

to the large number of results, studies reporting randomized clinical trials were excluded and the search results were refined using limits of human studies and English language. Additional studies were identified from reference lists of relevant articles.

### *Study selection*

After removal of duplicates, two reviewers (KG, TT) screened titles and abstracts for eligibility, and developed a list of full text articles through consensus. Two authors (TT, BS) considered the full texts of included articles and a final list of eligible articles was agreed. We contacted authors up to 3 times over a month to clarify study eligibility and/or acquire additional data.

### *Outcomes*

Multiple primary outcomes were used to capture different aspects of pain response<sup>25</sup>: (1) pain threshold (the point at which pain is first perceived), (2) pain tolerance (the point at which pain can no longer be tolerated), and (3) self-reported ratings of pain intensity/affect. Sensory threshold (the point at which sensation is first perceived) was included as a secondary outcome to investigate whether differences in pain perception were accompanied by differences in non-painful sensory perception.

### *Data Extraction*

Study data were extracted independently by two authors (TT, KG) using a standardized extraction form that we have used in several of our previous studies<sup>65,66</sup> but with a few, relatively minor adaptations for the topic of depression and pain perception, so coding protocols were very clear and unambiguous. Details were recorded for pain induction method, pain assessment outcome, depressed group (demographics, diagnostic method, symptom severity, antidepressant medication), control group (demographics), study design



and geographical location. We recorded group means and standard deviations for each pain outcome measure, or any other available information that would allow computation of effect size (see 'Meta-Analysis' section below). To minimize reporting bias, authors were also contacted for statistical details when non-significant findings were reported but in insufficient detail to allow computation of effect sizes.

When a study reported pain outcome data at different time points, we extracted averaged data if available, otherwise we extracted data at the first time point. When outcome data were collected at multiple stimulus intensities (usually applicable to electrical stimulation), the highest intensity was extracted as this was most likely to reliably evoke pain. When a study applied noxious stimulation to both left and right sides of the body, we used pain scores averaged across sites where possible, otherwise we extracted data from the right side as this was the most common site tested and may show greater sensitivity to detecting differences in pain response and increased homogeneity in our analyses<sup>4</sup>. From studies reporting pain data in participants before and after antidepressant treatment, we used unmedicated data for the overall pooled analyses, but we used data from treated patients for the medicated/unmedicated subgroup analysis. Finally, a few studies used sensory decision theory to yield two measures of pain threshold: response criterion and d-prime (sensory discrimination). Response criterion was abstracted as the data of interest, as this measure is the most closely related to verbally declared pain threshold used in the other included studies<sup>25</sup>.

#### *Methodological study appraisal*

Two authors (TT, BS) independently completed methodological quality assessment of included articles using the case-control Newcastle Ottawa Scale<sup>74</sup> (NOS). If any

disagreement arose, a third author (CC) was available for mediation. The NOS provides an assessment of the methodological quality of non-randomized trials and its content validity and reliability have been established. Included studies are judged on 9 items across three key areas: selection of the participants, comparability of the participants, and outcomes. Each study receives an overall score for methodological quality of up to 9 points (one for each item) and scores of 5 and above are considered to reflect satisfactory study quality<sup>74</sup>.

### *Meta- analysis*

As we anticipated heterogeneity in effect sizes due to variation in important study characteristics typical in experimental pain research, a random effects model using the method of moments was chosen. This allows heterogeneity to be accounted for statistically and permits generalization to studies beyond those examined in the meta-analysis. Hedges's  $g$  was calculated as the effect size based on standardized differences in pain scores between participants with depression and controls. All analysis was performed using Comprehensive Meta-Analysis software (CMA, version 3). When computing Hedge's  $g$ , if a study used multiple pain inductions we used the averaged pain score, or if this was not available, we used scores for heat/cold or electrical modalities, as these were the most commonly reported (as the choice of these modalities might have some influence on the overall effect size, we also computed effect sizes for each stimulus modality separately in subgroup analysis). If a study reported data from participants before and after anti-depressant medication we included only unmedicated data for overall analyses. Analysis of pain ratings was performed only for studies where stimulation intensity was equivalent for both groups (i.e. equal time/temperature), to avoid confounding of differences in pain ratings with differences in stimulus intensity. Analysis was conducted as described below.

First, we compared pain scores in depressed vs. control groups for each primary outcome of (1) pain threshold, (2) pain tolerance and (3) pain ratings and for the secondary outcome of sensory threshold. Heterogeneity was examined with Cochran's Q and  $I^2$  statistics to assess inconsistency of effect sizes across all studies for each pain outcome<sup>28</sup>. Cochran's Q tests the assumption that all studies share a common effect size, with  $p < .05$  used here to indicate a difference in true effect size across compared studies.  $I^2$  provides an estimate of the proportion of the total variation in effect sizes across studies that can be attributed to genuine heterogeneity in effect size. Higgins et al.<sup>28</sup> suggest guidelines of 25%, 50% and 75% can be used as rough approximations for low, medium and high heterogeneity. Publication bias was assessed with a visual inspection of funnel plots and with the Begg-Mazumdar Kendall's tau<sup>8</sup> and Egger's bias test<sup>20</sup>. If we encountered publication bias, we calculated the trim and fill adjusted analysis<sup>17</sup> to remove the most extreme small studies from the positive side of the funnel plot, and recalculated the effect size at each iteration, until the funnel plot was symmetric around the new effect size.

Second, we conducted subgroup analysis for pain threshold and tolerance (limited data prohibited subgroup analysis of other outcomes). As a primary interest was to determine whether depressed vs. control group differences were influenced by stimulus modality, we conducted separate analyses for each modality. We used Cochran's Q to test for overall differences in effect size across modalities, and if significant, used follow-up Z-tests to compare each individual modality vs. every other modality<sup>11</sup>. We also performed separate analysis for medicated/unmedicated subgroups, and examined whether results were similar when restricting the sample to patients with major depressive disorder (MDD) only.

Third, we performed meta-regression analysis to examine whether group differences were influenced by mean study age, gender composition and magnitude of depressive symptoms in the depressed group. Generally, meta-regression was performed only when at least 10

studies were available for analysis<sup>29</sup>, although mean age for pain tolerance was also included as the 9 studies available closely approximated this guideline. Pseudo- $R^2$ , an index of the amount of estimated true heterogeneity in effect size that can be accounted for by the covariates was also computed. Separate meta-regression analyses were performed for each moderator variable.

Finally, for studies that assessed pain perception before and after antidepressant treatment, we pooled within-subject changes in each pain outcome measure using pre and post means and SDs for both groups in order to assess the effect of antidepressant treatment on pain measurements.

## RESULTS

### *Study characteristics*

Initial searches yielded 5095 unique hits including 4 records identified through manual searching of reference lists. After screening, 65 articles were retained for full text review of which 33 were excluded (see Figure 1). Altogether, 32 studies were retained for analysis (Table 1).

*Figure 1 here*

*Table 1 here*

Across the 32 retained studies there were 30 unique studies with an aggregated total of 1317 participants (depression  $n=641$ , control  $n=676$ ). The two non-unique studies<sup>48,62</sup> were linked to two companion papers<sup>56,63</sup> that used the same sample but provided different

outcome data. Twenty-five studies matched depressed and control samples for age/gender or reported no differences, 2 studies reported age/gender differences and 3 studies did not report comparisons. The mean age of the depressed samples was 39.3 years (24.5-59.7 years) and the mean gender composition was 74.0% female (26-100%). The mean illness duration, reported in 6 studies, was 8.7 years (2-19 years). For controls, the mean sample age was 38.0 years (23.9-53.7 years), with a mean gender composition of 71.4% female. Overall, 8 studies were conducted in North-America, 19 in Europe and 2 in South-America, with 1 study not specifying region. Studies most commonly used MDD only (k=21 studies), as the depressed group, followed by other diagnosed depressive disorders, e.g. persistent depressive disorder (k=5), and depressive syndrome based on depression severity assessed with a screening questionnaire, e.g. the Beck Depression Inventory (BDI)<sup>7</sup> (k=4). Depressive symptoms were measured in 24 studies, with the most commonly used measure the Hamilton Depression Rating Scale (HAM-D)<sup>26</sup> (k=13), followed by the BDI (k=10). Antidepressant treatment status was reported as either unmedicated (k=16), fully medicated (k=6) or mixed medicated/unmedicated (k=7), with two studies providing data on the same sample before and after antidepressant treatment<sup>4,5</sup>. Three studies did not report medication status. A study average of 31.4% (range 0-100) of depressed patients were treated with antidepressants at baseline (19 studies provided this information). The following pain induction methods were used: heat (k=17), cold (k=7), electrical (k=8), ischemia by tourniquet procedure (k=6), pressure (k=4), laser (k=1).

Mean total NOS score across studies was 5.1 with a range of 4-6 (Table 1). Individual quality criteria least frequently addressed included participant selection and experimenter blinding. More specifically, several studies employed hospital controls and many studies provided inadequate descriptions of recruitment procedures for depressed participants and/or controls, introducing the potential for selection bias or non-representativeness. In addition,

most studies did not report use of experimenter blinding, inviting the possibility of bias in the assessment of pain, although the influence of this might be expected to be minimal given the type of pain assessments used. Intra-class correlations and Cohen's Kappa indicated adequate inter-rater agreement for total NOS scores,  $ICC(A, 2)=0.51$ , and excellent<sup>36</sup> agreement on coding decisions for categorical ( $Kappa = 0.87-1.00$ ) and continuous ( $ICCs= 0.89-1.00$ ) data, except for extracted SDs ( $ICC=0.05-0.07$ ). The latter was due to two articles misreporting SEMs as SDs and was resolved by further statistical investigation, with 100% agreement on all decisions reached after consultation with the third rater (CC).

### Meta-analysis results

Details of all meta-analysis results are presented in Table 2, with key findings for each outcome measure summarized below.

#### 1. Pain threshold

In the pooled analysis, 25 studies including 567 people with depression and 587 controls demonstrated a higher overall pain threshold (i.e., reduced pain) in people with depression compared to controls,  $g=0.32$ , 95%CI [0.05, 0.59],  $p=0.02$ . There was no evidence of publication bias (Egger=1.0,  $p=0.68$ ; Begg=0.15,  $p=0.69$ ). However, statistically significant ( $Q=117$ ,  $p<.01$ ) and high ( $I^2=77\%$ ) heterogeneity was observed, with effect sizes varying across studies in both magnitude and direction (Figure 2). Given this variation, subgroup analyses were conducted to identify possible moderating variables.

*Figure 2 here*

*Subgroup analysis of pain threshold*

Individuals with depression exhibited *reduced* pain threshold (i.e., increased pain) in all 5 studies that employed ischemic pain induction ( $g=-0.81$ , 95%CI  $[-1.39, -0.24]$ ,  $p=.006$ ), reversing the pattern of results seen for other pain induction methods (Table 2). Cochran's Q revealed a significant overall difference in effect size across modalities ( $Q=10.2$ ,  $p=.017$ ), with Z-tests showing effect size to be significantly different for ischemic compared to other modalities ( $z's=5.25-6.98$ ,  $p<.0001$ ), with no other significant differences between other modalities.

When MDD-only studies ( $k=17$ ) were examined, significantly greater pain threshold was observed for depressed participants relative to controls ( $g=0.38$ , 95%CI  $[0.02, 0.75]$ ,  $p=0.03$ ). The same was true for unmedicated ( $g=0.32$ , 95%CI  $[0.01, 0.70]$ ,  $p=0.04$ ,  $k=15$ ), but not in medicated individuals ( $g=0.16$ , 95%CI  $[-0.55, 0.89]$ ,  $p=0.63$ ,  $k=5$ ).

Although subgroup analyses indicate that effect sizes may be influenced by stimulus modality, estimates of  $I^2$  (Table 2) did not noticeably diminish (with the possible exception of the cold stimulus), suggesting that considerable heterogeneity remains even when stimulus modality is accounted for.

*Meta-regression of pain threshold*

In meta-regression analysis, depressive symptom severity (analyzing only studies that used the HAM-D, which was most commonly employed rating scale, in order to increase homogeneity of the findings), sex, age or study quality (NOS scores) were not significantly related to group differences in pain threshold ( $k=12-25$  studies,  $\beta=.00-.24$ ,  $p=0.14-0.99$ ); see Table S2 for full results. Meta-regression was not performed on duration of illness as only 6 pain threshold studies provided this data.

## 2. Pain tolerance

Pooling data across 10 studies from 199 people with depression and 215 controls, no overall difference in pain tolerance was observed,  $g=0.09$ , 95% CI  $[-0.39, 0.57]$ ,  $p=0.71$  (figure S1). There was no evidence of publication bias (Begg=-0.26,  $p=0.28$ , Egger=-4.1,  $p=0.16$ ). Similar to pain threshold, a high level of heterogeneity was observed ( $I^2=71\%$ ), so subgroup analyses were conducted.

### *Subgroup analysis of pain tolerance*

Depressed participants exhibited significantly reduced pain tolerance (i.e., increased pain) in response to ischemic pain induction ( $g=-0.76$ , 95% CI  $[-1.04, -0.47]$ ,  $p<0.001$ ,  $k=6$ ), but without significant differences observed for other pain modalities (Table 2). Cochran's Q showed a significant difference in effect sizes across modalities overall ( $Q=12.64$ ,  $p<0.01$ ). Z-tests found effect sizes to be significantly different for ischemic vs. other modalities ( $z's=4.39-6.24$ ,  $p<0.0001$ ), with no other paired comparison being statistically significant. As with pain threshold, although significant differences in effect sizes across modalities were observed, heterogeneity was not notably diminished when subgroups were examined separately, with the exception of ischemic pain ( $I^2=0$ ).

The lack of overall group differences in pain tolerance in the pooled sample was confirmed in the subgroup of unmedicated participants,  $g=0.02$ , 95% CI  $[-0.54, 0.56]$ ,  $p=0.97$ ,  $k=7$ , (only two studies of tolerance with medicated participants were available, so these were not examined). When studies with major depressive disorder only samples were analyzed, depressed participants showed higher tolerance than controls, but this finding did not reach significance ( $g=0.41$ , 95% CI  $[-0.18, 0.99]$ ,  $p=0.18$ ,  $k=4$ ).



*Meta-regression of moderators of pain tolerance*

Although no overall group differences in pain tolerance were found in the previously reported meta-analysis, meta-regression was conducted to examine whether group differences might be influenced by age, gender or study quality. However, differences between depressed and control groups were not significantly moderated by any of these variables (Table S2).

*3. Pain ratings*

Pooling data from 155 people with depression and 193 controls across 8 studies yielded no significant between-group differences in ratings of pain intensity ( $g=0.00$ , 95% CI  $[-0.37, 0.37]$ ,  $p=0.97$ ). Similarly, pooling data from 4 studies, including 99 people with depression and 118 controls, demonstrated no significant group differences in pain affect ( $g=-0.37$ , 95% CI  $[-1.29, 0.55]$ ,  $p=0.43$ ).

*4. Sensory threshold*

Pooling data from 9 studies, including 178 people with depression and 178 controls, sensory threshold was significantly higher in people with depression,  $g=0.35$ , 95% CI  $[0.08, 0.62]$ ,  $p=0.01$  (Figure S2). There was some evidence of publication bias (Egger=4.7,  $p=0.05$ ), but the effect size remained unchanged when we calculated Duval and Tweedie trim and fill method ( $0.35$ , 95% CI  $[0.08, 0.62]$ ).

Table 2

*Changes in pain response before and after medication*

Two studies<sup>4,5</sup> investigated differences in pain threshold, tolerance and sensory threshold using heat induction among a total of 42 people with MDD before and after antidepressant medication and 42 matched controls at equivalent before/after time points. Following antidepressant medication, the difference in pain threshold between depressed and control participants was significantly reduced ( $g=-0.57$ , 95% CI [-1.01, -0.12],  $p=0.01$ ) as was sensory threshold ( $g=-0.44$ , 95% CI [-0.88, -0.01],  $p=0.04$ ). No significant effects were observed for pain tolerance ( $g=0.25$ , 95% CI [-0.18, 0.69],  $p=0.20$ ) after antidepressant medication.

**Discussion**

The current review is the largest and most comprehensive meta-analysis investigating responses to experimentally-induced pain in people with depression vs. healthy controls. Several key findings emerged from the study: (1) Pooled mean pain threshold ( $g=0.32$ ) and sensory threshold ( $g=0.35$ ) were higher in people with depression (indicating diminished pain) although considerable study heterogeneity suggested little evidence of a generalized, uniform effect of depression; (2) Overall pain tolerance and pain ratings did not differ between depressed individuals and controls; and (3) The direction of the relationship between depression and pain appeared to be influenced by stimulus modality, with depressed individuals showing *increased* pain for ischemic stimulation, a reversal of the pattern found for other modalities.

Our findings of elevated overall pain threshold in depression confirm and extend preliminary findings from a previous meta-analysis of 6 experimental studies<sup>16</sup>, but in a much larger pool of 25 pain threshold studies. Small overall effect sizes were observed in both the current ( $g=0.32$ ) and previous meta-analysis ( $d=0.38$ ). Additionally, we were able to examine a wider range of assessment measures than the previous review, including pain tolerance. Although there were fewer studies of tolerance available relative to threshold studies, there was little

evidence of any link between depression and suprathreshold pain, with no significant differences in pain tolerance ( $g=0.09$ ) found. These findings suggest that depression may be associated with a general decreased sensitivity to low intensity stimulation, but not to higher intensity stimulation (e.g. that producing tolerance level of pain). The possibility of increased thresholds in depression is consistent with attentional pain processing models<sup>19</sup>. These state that limited attentional resources are competed for by painful and other, non-painful stimuli. If greater attention is devoted to non-painful stimuli (e.g. environmental stimuli/internal thoughts), as has been observed in depression<sup>45</sup>, this should reduce pain by denying it attentional resources; especially for mild pain, which is of relatively low attentional priority. Dickens et al.<sup>16</sup> pointed out that these models would explain the increased pain threshold they found in depressed participants, but should also predict little difference for higher intensity pain which commands greater attention. While the authors were unable to test this hypothesis due to lack of tolerance data, this hypothesis appears to be confirmed by our results which offer further support for current attentional models.

An important caveat in interpreting the association between depression and pain threshold is that considerable heterogeneity was observed. Studies varied both in the magnitude and direction of effects, suggesting that conclusions regarding a generalized effect of depression on pain perception are overly simplistic, and that any such effect may depend upon complex constellations of other moderating factors. Based on the current findings, diminished pain perception cannot be considered a reliable marker of depression.

A key finding was that the depression-pain link appears to be strongly influenced by the type of pain induced. Whereas depression was associated with reduced or no alteration of pain for most modalities (e.g., heat, cold, electrical), depressed participants exhibited *increased* pain in response to ischemic induction. These differences in responses across modalities are consistent with the wider pain literature exhibiting typically weak

relationships of pain across different induction methods<sup>49</sup>. The relationship between other psychological variables, such as anxiety sensitivity, with pain have also been shown to vary across modality<sup>70</sup>. The fact that experimental studies frequently indicate decreased pain in depression contrasts with clinical studies, where depressed patients often report more pain complaints<sup>2,15</sup> with increased depression associated with increased pain severity<sup>35</sup>. Given that experimental and clinical pain differ on several key dimensions<sup>43</sup> and are often weakly associated<sup>12</sup>, it may be that experimental findings simply do not generalize outside of the laboratory. However, the fact that depression is associated with increased pain for ischemic (and clinical) pain but with decreased/unaltered pain for other inductions, could contribute to our understanding of the discrepancy between experimental and clinical findings. First, experimental studies typically rely on exteroceptive stimulation of the skin<sup>44</sup> (the cold pressor also provides stimulation of both deeper and peripheral structures, although stimulation of deeper structures is far less pronounced, and several studies examined here used a skin contact thermode to induce cold). Both ischemia and clinical pain, however, are evoked through interoceptive pathways by nociceptors innervating deep structures<sup>57</sup> (e.g. muscle, joints), involve greater C-fiber recruitment and are subject to greater modulation from descending pain inhibitory pathways<sup>57</sup>. Second, pain is a multidimensional experience involving sensory, cognitive and affective components<sup>43</sup>, and it may be that depressed individuals react more negatively to pain with a stronger affective component. Clinical pain is more distressing than typical experimental pain, and ischemic pain is often more severe, diffuse and uncontrollable than noxious skin stimulation<sup>43</sup>, so may produce greater negative affect (although too few studies recorded pain affect to evaluate this statistically). While the suggestion that the depression-pain link may be influenced by pain affect or its interoceptive/exteroceptive origin is necessarily speculative, it represents a plausible explanation for the discrepancies in findings across different modalities and clinical reports that warrant further empirical investigation.

If any effects of depression are influenced by modality, pinpointing possible underlying mechanisms is largely speculative, given a lack of appropriate empirical data. One possible explanation is provided by Lautenbacher and Krieg's global theory of pain processing in psychiatric disorders<sup>37</sup>, and speculates that neurotransmitter dysfunction in depression affects pain perception in two ways. First, by diminishing spinal and subcortical processing which reduces processing of all sensory input therefore elevating sensory/pain thresholds. Second, by disrupting descending pain pathways which inhibit sustained or endogenous (e.g., ischemic) pain, thus heightening pain of endogenous origin. However, while there is some evidence that the areas of the brain involved in mood regulation also regulate pain pathways<sup>77</sup>, more empirical data are needed to convincingly demonstrate that depression selectively modulates pain processing in this way.

There is also tentative evidence to suggest that any putative effect of depression on pain could be influenced by anti-depressant medication. The two prospective studies found that the greater sensory and pain thresholds exhibited by depressed patients relative to controls were diminished following antidepressant treatment. In addition, the increased pain threshold observed in depressed participants was significant only in the unmedicated and not in the anti-depressant medicated group. However, given the minimal difference in effect size and the greater power of the unmedicated analysis from more available studies, this finding must be considered entirely preliminary. Nevertheless, since several neurotransmitters believed to be involved in the pathophysiology of depression are also involved in pain, e.g. serotonin, noradrenalin<sup>2</sup>, it would perhaps be unsurprising that modulation of these neurotransmitters might restore not only mood but also sensory/pain threshold gating. Further data is, however, clearly needed to support any potential effect of anti-depressant medication.

Several limitations of the current review should be noted. First, considerable study heterogeneity was observed which could not be resolved by study differences in symptom severity, gender, age or study quality. Given this heterogeneity, caution in interpreting findings must be applied, especially where confidence intervals are relatively broad. Additionally, although significant differences in effect size across stimulus modalities were observed, there is little evidence that modality offers any substantive resolution of this heterogeneity. It seems likely that important moderators of the relationship between depression and pain perception exist (e.g., methodological, use/non-use of chronic pain patients) but remain unidentified. Second, while factors such as the endogenous nature of ischemic pain represent one theoretically plausible reason for differences across ischemic and other stimuli, other confounding characteristics (e.g. stimulus duration) may offer alternative explanations for these differences. Third, fewer studies investigating pain tolerance ( $k=10$ ) were available for analysis compared to pain threshold ( $k=25$ ). The lack of significant overall tolerance differences is unlikely to be attributable to reduced power, however, as the aggregated tolerance sample was still large ( $N=375$ ) and the effect size close to zero. Finally, only experimental pain studies were examined and therefore the current findings may have limited generalizability to clinical pain.

Further research should be conducted to help elucidate reasons for inconsistency across study findings and identify potential moderators, such as pain duration<sup>54</sup> and negative pain affect<sup>30</sup>, which have been suggested to influence the relationship between depression and chronic pain. In addition, measurement and/or careful control of variables likely to differ across ischemic and other pain inductions (e.g., stimulus contact time and negative affect), could help explain why differences across modalities were observed. Additional studies employing within-group designs, where individual variability can be controlled, could directly compare ischemic and cutaneous pain inductions to provide further supporting evidence for

the role of modality. Future studies should also attempt to improve study quality by striving to acquire representative samples for depressed and control participants (e.g. avoiding hospital controls) and providing clearer descriptions of recruitment procedures.

In summary, this is the largest and most comprehensive meta-analysis of experimental pain induction studies in individuals with depression to date and suggests two key findings. First, there is some evidence that depression may be associated with an overall reduced perceptual sensitivity to low, but not high intensity stimulation. However, this overall effect is relatively small and considerable variation in study findings indicates that diminished pain may only be evident under certain, partly unidentified conditions. Second, any putative impact of depression appears to be strongly influenced by modality, with depressed participants showing *increased* pain in response to ischemic stimulation, but reduced or unaltered pain perception in response to other stimulus modalities. This finding is consistent with theory proposing different neural pathways for interoceptive and cutaneous-based pain and suggests that depression could affect these pathways differentially. Overall, these findings provide support for a relationship between depression and pain, but indicate that this relationship is complex and deserves further research that pays particular attention to variability due to stimulus intensity and modality as well as additional moderating variables.

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Figure 1. Prisma flow diagram

Figure 2. Pain threshold in depressed vs. control participants

Figure S1. Pain tolerance in depressed vs. control participants

Figure S2. Sensory threshold in depressed vs. control participants

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Table 1. Summary of included studies

Author	Location & Setting	Depression group	Antidepressant Treatment	Control participants	Pain modality	Pain measure	NOS scores
<i>Zambito Marsala et al 2015</i> <sup>76</sup>	Italy, setting not stated	N=27, MDD, 26% female, age=47.2 years, HAM-D: 22.6. Pain screening <sup>c</sup> =yes	Unmedicated	N=27, 26% female, age=53.7	Electrical	Sensory threshold Pain threshold Pain tolerance	5
<i>Rodriguez-Raecke et al 2014</i> <sup>a,56</sup>	Germany, inpatient	N=21, MDD, 38% female, age=36.1 years. Pain screening =yes	Mixed	N=21, 71% female, age=36.8	Heat	Pain threshold fMRI	6
<i>Muhtz et al 2013</i> <sup>a,48</sup>	Germany, inpatient	N=22, MDD, 27% female, age=36.3 years. Pain screening =yes	Mixed	N=33, 64% female, age=33.3	Heat	Intensity rating	6
<i>Bär et al 2011</i> <sup>5</sup>	Germany, setting not stated	N=22, MDD, 77% female, age=42.2 years, Baseline MADRS: 25.36, BDI: 22.5; 6 weeks: MADRS: 9.41, BDI: 11.36. Participants scoring >3 on present pain excluded	Unmedicated/ Medicated (Duloxetine)	N=22, 77% female, age=42.5	Heat Ischemic	Sensory threshold Pain threshold Pain tolerance Intensity rating	6
<i>Normand et al 2011</i> <sup>50</sup>	Canada, setting not stated	N=26, MDD, 61% female, age=46.5 years. Pain screening =yes	Medicated	N=40, 60% female, age=45.2	Heat Cold	Pain threshold Intensity rating	5
<i>Terhaar et al 2011</i> <sup>69</sup>	Germany, inpatient	N=27, MDD, 78% female, age=38.5 years, BDI: 23, HAM-D: 23.2. Pain screening =yes	Unmedicated	N=27, 78% female, age=39.5	Laser	Sensory threshold Pain threshold	5
<i>Euteneuer et al 2011</i> <sup>21</sup>	Germany, outpatient	N=37, MDD, 56.7% female, age=33.5 years, BDI: 21.46, SCL 90-R GSI: 1.03. Pain screening =yes	Mixed	N=48, 63% female, age=35.8	Pressure	Pain threshold	4
<i>Strigo et al 2010</i> <sup>61</sup>	US, setting not stated	N=15, MDD, 80% female, age=24.5 years, BDI-2: 27.8. Pain screening =yes	Unmedicated	N=17, 59% female, age=24.3	Heat	Pain threshold (for 'moderate' pain)	5

Author	Location & Setting	Depression group	Antidepressant Treatment	Control participants	Pain modality	Pain measure	NOS scores
<i>Klatzkin et al 2010</i> <sup>33</sup>	US, setting not stated	N=10, PMDD, 100% female, age not stated. Pain screening =yes	Unmedicated	N=18, 100% female, age not stated	Cold pressor Ischemic	Pain threshold Pain tolerance Intensity rating Unpleasantness	5
<i>Lopez-Sola et al 2010</i> <sup>41</sup>	Spain, setting not stated	N=13, MDD, 85% female, age=44.6 years, HAM-D: 21.3, Pain screening =yes	Medicated	N=20, 75% female, age=47.2	Heat	Intensity Unpleasantness fMRI	5
<i>Boettger et al 2010</i> <sup>10</sup>	Germany, inpatient	N=22, MDD, % female not stated, age=41 years, BDI: 24.2, HAM-D: 23.0. Pain screening =not stated	Mixed	N=20, % female not stated, age=40	Electrical	Intensity rating EEG	5
<i>Terhaar et al 2010</i> <sup>68</sup>	Germany, inpatient	N=25, MDD, 100% female, age=49.8 years, BDI: 18.8, MADRS: 21.7. Pain ratings>2 was exclusion criterion	Mixed	N=25, 100% female, age=48.3	Heat	Pain threshold	5
<i>Schwier et al 2010</i> <sup>58</sup>	Germany, setting not stated	N=20, MDD, 85% female, age=37.2 years, HAM-D: 19.4, BDI: 24.3. Pain screening =yes	Unmedicated	N=20, 85% female, age=34.8	Cold	Pain threshold	5
<i>Strigo et al 2008</i> <sup>b,62</sup>	US, setting not stated	N=15, MDD, 80% female, age=24.5 years, BDI: 27.8. Pain screening =yes	Unmedicated	N=15, 80% female, age=23.9	Heat	Pain threshold Intensity rating Unpleasantness rating	6
<i>Strigo et al 2008</i> <sup>b,63</sup>	US, setting not stated	N=15, MDD, 80% female, age=24.5 years, BDI: 27.8. Pain screening =yes	Unmedicated	N=15, 67% female, age=24.3	Heat	fMRI	5
<i>Klaunberg et al 2008</i> <sup>34</sup>	Germany, inpatient	N=25, Mixed diagnosis types, 60% female, age=48 years, HADS (depression): 13, HADS (anxiety): 13. Pain screening =not stated	Medicated	N=25, 67% female, age=47.	Cold Heat Mechanical (von Frey) Mechanical (pressure)	Sensory threshold Pain threshold Intensity rating	5



Author	Location & Setting	Depression group	Antidepressant Treatment	Control participants	Pain modality	Pain measure	NOS scores
<i>Bär et al 2007</i> <sup>6</sup>	Germany, inpatient	N=13, MDD, 100% female, age=35.9 years, HAM-D: 23.7, BDI: 26.5, STAI-X1: 42.0, STAI-X2: 46.1. Pain screening: all participants pain ratings<2	Unmedicated	N=13, 100% female, age=34.3.	Heat	Pain threshold fMRI	5
<i>Bär et al 2005</i> <sup>3</sup>	Germany, setting not stated	N=30, MDD, 77% female, age=44.9 years, HAM-D: 21.9. Pain screening =yes	Mixed (mostly medicated)	N=30, 77% female, age=44.7.	Heat Electrical Ischemic	Pain threshold Pain tolerance	5
<i>Spernal et al 2003</i> <sup>60</sup>	Germany, inpatient	N=21, MDD, 57% female, age=39 years, HAM-D: 23.6, HAM-A: 21.2. Pain screening =not stated	Unmedicated	N=20, 60% female, age=34.6	Heat Cold pressor Pressure	Pain threshold	5
<i>Suarez-Roca et al 2003</i> <sup>67</sup>	Venezuela, setting not stated	N=11, Dysthymic, 91% female, age=32.4 years, Zung's index: 60. Pain screening =not stated	Not stated	N=19, 79% female, age=31.4	Ischemic	Pain tolerance Intensity rating	5
<i>Bär et al 2003</i> <sup>4</sup>	Germany, setting not stated	N=20, MDD, 70% female, age=40.1 years, BDI: 22.8, HAM-D: 28.1 Pain screening =not stated	Unmedicated/ Medicated	N=20, 70% female, age=38.8	Heat	Sensory threshold Pain threshold Pain tolerance	6
<i>Lautenbacher et al 1999</i> <sup>39</sup>	Germany, inpatient	N=13, MDD, 62% female, age=35.4 years, HAM-D: 23.8, HAM-A: 23.2. Pain screening =not stated	Unmedicated	N=13, 62% female, age=32.9	Pressure Cold pressor Heat	Pain threshold	5
<i>Pinerua-Shuhaibar et al 1999</i> <sup>52</sup>	Venezuela, setting not stated	N=11, Dysthymic, 91% female, age=32 years, Zung: 59. Pain screening =not stated	Unmedicated	N=32, 47% female, age=32	Ischemic	Pain threshold Pain tolerance Intensity rating Unpleasantness rating	4
<i>Marazziti et al 1998</i> <sup>42</sup>	Italy, Outpatient	N=13, MDD, 69% female, age=43.6 years, HAM-D: 18.3, SAD: 71.2. Pain screening =not stated	Mixed (mostly unmedicated)	N=13, 38% female, age=30.7	Electrical	Sensory threshold Pain tolerance	4



Author	Location & Setting	Depression group	Antidepressant Treatment	Control participants	Pain modality	Pain measure	NOS scores
<i>Fillingim et al 1995</i> <sup>23</sup>	US, setting not stated	N=7, PDD, 100% female, age=35.1 years. Pain screening =yes	Unmedicated	N=11, 100% female, age=31.4	Heat Ischemic	Pain threshold Pain tolerance	5
<i>Dworkin et al 1995</i> <sup>18</sup>	US, Inpatient	N=26, MDD, 73% female, age=42.4 years. Pain screening =not stated	Not stated	N=32, 50% female, age=46.6	Heat	Pain threshold	5
<i>Lautenbacher et al 1994</i> <sup>38</sup>	Germany, setting not stated	N=20, MDD, 40% female, age=36.9 years, HAM-D: 25.1. Pain screening =not stated	Mixed	N=20, 40% female, age=36.2	Heat Pressure	Pain threshold Sensory threshold	5
<i>Adler et al 1993</i> <sup>1</sup>	Germany, setting not stated	N=16, MDD, 56% female, age=33.2 years, HAM-D: 26.7. Pain screening =not stated	Unmedicated	N=16, %female not stated, age not stated	Electrical	Sensory threshold Pain threshold	4
<i>Otto et al 1989</i> <sup>51</sup>	US, setting n/a	N=16, BDI=>16 (depression), 100% female, age not stated, BDI: 25.9. Pain screening =not stated	Unmedicated	N=16, 100% female, age not stated	Cold pressor	Pain threshold Pain tolerance Intensity rating	5
<i>Ben-Tovin et al 1981</i> <sup>9</sup>	Location not stated, Inpatient	N=8, Primary affective disorder: depressed type, 100% female, age=59.7 years, HAM-D: 18.8. Pain screening =not stated	Medicated	N=8, 100% female, age=37.2	Electrical	Sensory threshold Pain threshold	6
<i>Davis et al 1979</i> <sup>14</sup>	US, inpatient	N=66, Depressed (Bunney-Hamburg rating scale, global mania => 2), 61% female, age=38 years. Pain screening =not stated	Unmedicated	N=48, 65% female, age=38.2	Electrical	Pain threshold Unpleasantness rating EEG	5
<i>von Knorring et al 1974</i> <sup>72</sup>	Sweden, setting not stated	N=45, Depressive disorders, % female not stated, age not stated. Pain screening =not stated	Not stated	N=20, % female not stated, age not stated	Electrical	Pain threshold Pain tolerance	5

Author	Location & Setting	Depression group	Antidepressant Treatment	Control participants	Pain modality	Pain measure	NOS scores
<b><u>TOTAL</u></b>	Studies=32 (Unique=30); Region: N America=8, Europe=19, S America 2, Not stated=1; Setting: Outpatient=2 Inpatients=11, Unclear=17	N=641 participants with depression, mean age= 39.3 years, females=74.0%. 17 studies screened for chronic pain, 15 studies did not.	Antidepressant-treated=6; Unmedicated= 16; Mixed = 7; Not stated =3	N=676 controls, mean age=38.0 years, females=71.4%	Heat=17; Cold=7; Pressure=4; Ischemic=6; Laser=1; Electrical=8; Mechanical=1	Pain threshold=26; Pain intensity=11; Pain tolerance=11; Sensory threshold=9; Pain unpleasantness=5; fMRI=4; EEG=2	

**Key:** BDI: Beck Depression Inventory; EEG: Electroencephalography; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Rating Scale for Depression; MADRS: Montgomery Asberg Depression Rating Scale; MDD: Major Depressive Disorder; PMDD: Premenstrual Dysphoric Disorder; SAD: Scala di Autovalutazione per la Depressione; STAI: State-Trait Anxiety Inventory.

<sup>a,b</sup> Identical superscript symbol indicates same sample used across two studies (but different pain outcomes reported in each)

<sup>c</sup> Screening for chronic pain

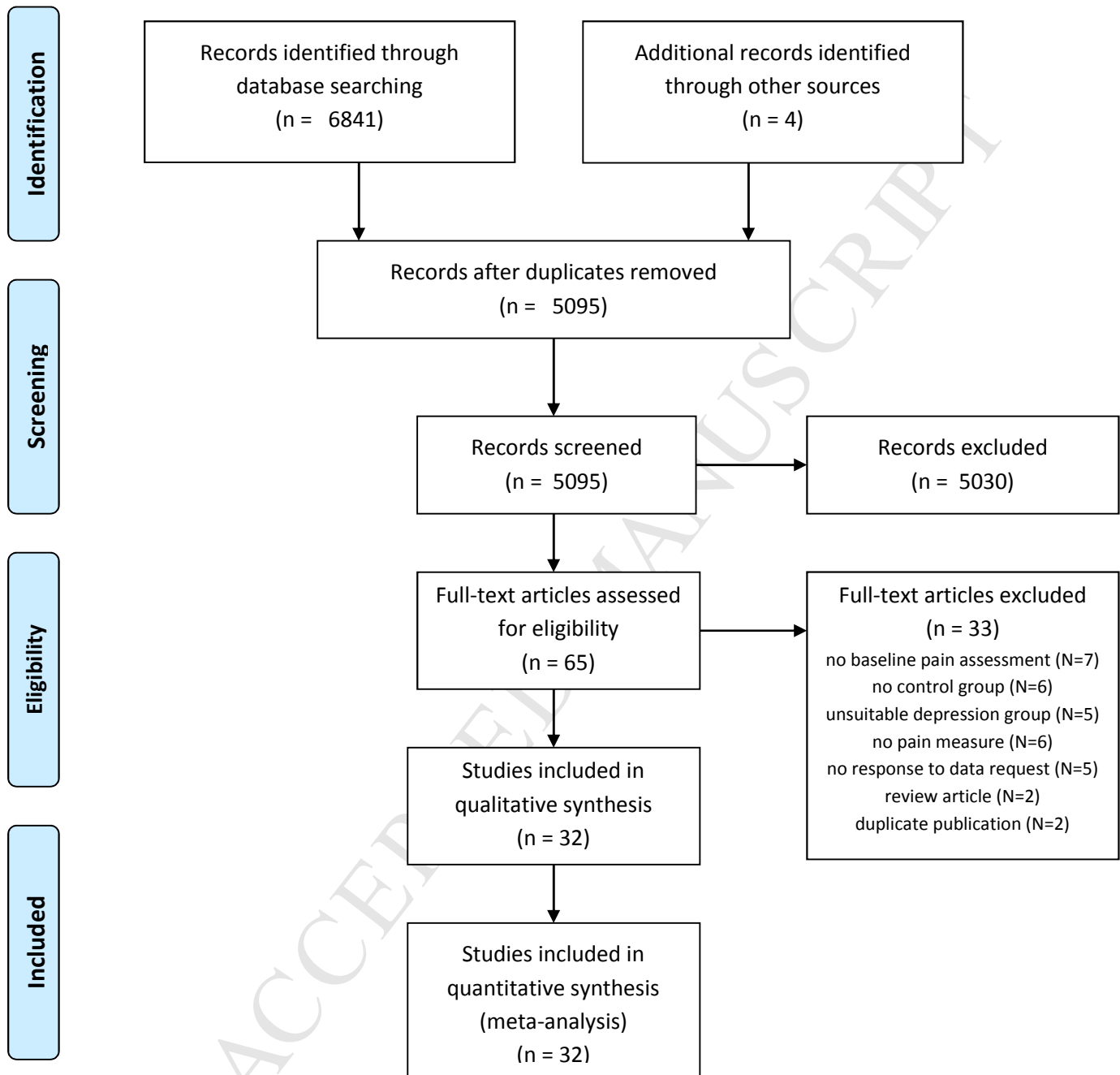
Table 2. Meta-analysis results of experimental pain in depression versus controls (positive Hedges g indicates reduced pain sensitivity in depression)

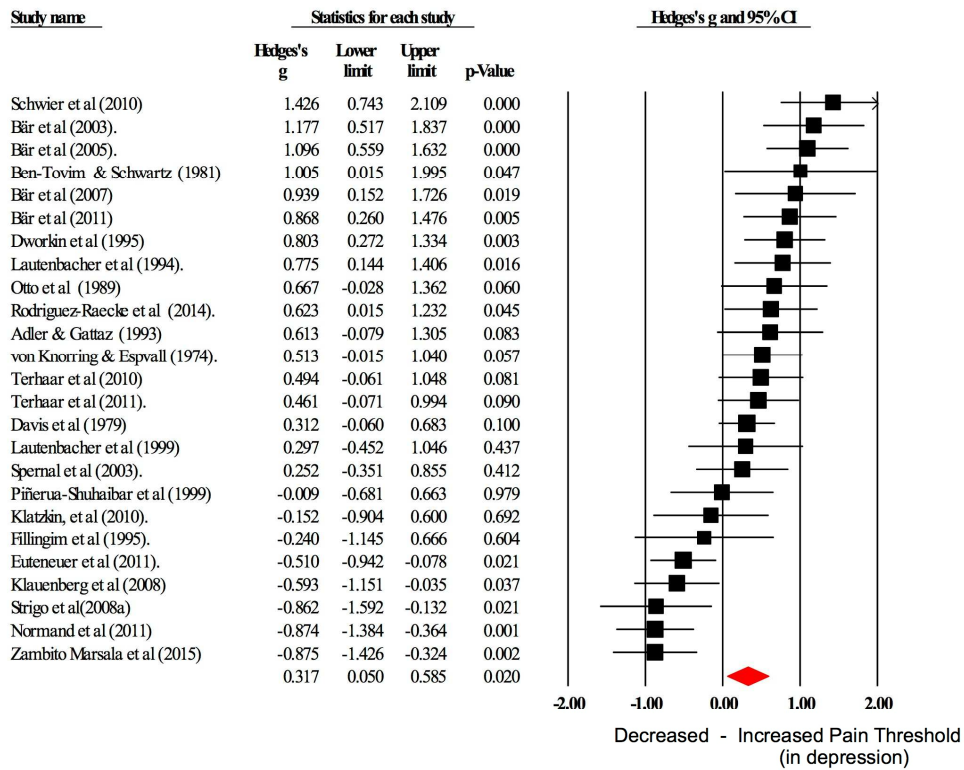
	Number of studies	Number of participants		Meta-analysis			Heterogeneity		Publication bias		
		Depression	Control	Hedges g	95% CI		P value	Q (p value)	I <sup>2</sup>	Begg	Egger
PAIN THRESHOLD											
Main analysis	25	567	587	0.32	0.05	0.59	0.02	117, p<0.01	77	0.15, p=0.69	1.0, p=0.68
MDD only	17	379	409	0.38	0.02	0.75	0.03	101, p<0.01	83	0.13, p=-0.56	1.4, p=0.54
Medication											
Unmedicated	15	304	318	0.32	0.01	0.70	0.049	54, p<0.01	77	-0.06, p=0.89	0.4, p=0.88
Medicated	5	101	115	0.16	-0.55	0.89	0.63	33, p<0.01	89	0.24, p=0.56	0.3, p=0.61
Modality											
Heat	14	284	307	0.35	-0.04	0.74	0.07	72, p<0.01	77	0.31, p=0.71	0.8, p=0.51
Cold	6	105	112	0.30	-0.38	0.97	0.38	30, p<0.01	34	0.50, p=0.48	1.0, p=0.46
Electrical	6	192	149	0.37	-0.15	0.88	0.16	25, p<0.01	80	-0.20, p=0.57	0.8, p=0.63
Ischemia	5	80	113	-0.81	-1.39	-0.24	0.006	13, p<0.01	71	-0.56, p=0.26	-1.0, p=0.23
PAIN TOLERANCE											
Main analysis	10	199	215	0.09	-0.39	0.57	0.71	50, p<0.01	72	-0.26, p=0.28	-4.1, p=0.16
MDD only	4	99	99	0.41	-0.18	0.99	0.18	9, p=0.03	64	-0.16, p=0.73	-2.4, p=0.68
Medication											
Unmedicated	7	113	146	0.02	-0.54	0.56	0.97	28, p<0.01	77	0, p=1	-1.9, p=0.71
Pain Modality											
Heat	4	79	83	0.51	-0.13	1.15	0.12	11, p=0.01	45	-0.8, p=0.12	-13, p=0.08
Cold	2	26	34	0.33	-1.08	1.58	0.79	5, p=0.21	85	N/A	N/A
Electrical	3	77	77	0.15	-0.75	1.05	0.74	11, p=0.03	83	0, p=1	-5.0, p=0.68
Ischemia	6	91	132	-0.76	-1.04	-0.47	<0.001	5, p=0.36	0	0.13, p=0.70	2.6, p=0.38
PAIN AFFECT	4	99	118	-0.37	-1.29	0.55	0.43	31, p<0.01	90	-0.16, p=0.73	-5.6, p=0.49
PAIN INTENSITY	8	155	193	0.00	-0.37	0.37	0.97	21, p<0.01	66	-0.3, p=0.90	-3.8, p=0.40
SENSORY THRESHOLD	9	178	178	0.35	0.08	0.62	0.01	12, p=0.12	36	0.66, p=0.11	4.7, p=0.05

**Key:** MDD= major depressive disorder, N/A= not applicable (<3 studies publication bias not applicable).

Bolded values: significant effect size results

Figure 1. PRISMA flow diagram





**Highlights**

- Meta-analysis of 32 experimental pain studies compared depressed vs. controls
- Higher overall pain threshold in depression but strong heterogeneity evident
- No differences in pain tolerance
- Depression and pain link may be dependent upon type of pain stimulation